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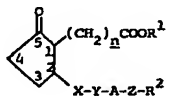
(54) CYCLOPENTANE DERIVATIVES

(71) We, MAY & BAKER LIMITED, a British Company of Dagenham, Essex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to new cyclopentane derivatives possessing pharmacological properties.

According to the present invention, there are provided the new cyclopentane derivatives of the general formula: —



I

[wherein R^1 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 12 (for example from 1 to 4 or from 7 to 12) carbon atoms, R^2 represents an aryl or heterocyclyl group (for example a phenyl, naphthyl, furyl or thienyl group, and preferably a phenyl, naphthyl or thienyl group), which may be substituted by one or more substituents selected from halogen (e.g. fluorine, chlorine or bromine) atoms, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms, trihalomethyl (e.g. trifluoromethyl) groups, alkenyl groups containing from 2 to 4 carbon atoms, phenyl groups, alkoxy group containing from 1 to 4 carbon atoms, hydroxy groups, nitro groups, cyano groups, carboxy groups, alkoxycarbonyl groups wherein the alkoxy moiety contains from 1 to 4 carbon atoms, hydroxymethyl groups, alkoxymethyl groups wherein the alkoxy moiety contains from 1 to 4 carbon atoms, sulphino groups, alkylsulphonyl groups wherein the alkyl moiety contains from 1 to 4 carbon atoms, and sulphamoyl, carbamoyl, N-aminocarbamoyl, amidino, amino and hydroxyamino groups, each such nitrogen-containing group optionally being substituted by one or more alkyl groups each containing from 1 to 4 carbon atoms, *n* represents 5, 6, 7 or 8, preferably 6, and either (i) A represents a straight- or branched-alkylene chain containing from 1 to 12, preferably from 1 to 7, carbon atoms, X represents an ethylene or *trans*-vinylene group, Y represents a carbonyl group or a group —CH(OR³)— (wherein R^3 represents a hydrogen atom or a carboxylic acyl group, for example a straight- or branched-chain alkanoyl group containing from 1 to 6 carbon atoms or a benzoyl group), and Z represents a direct bond or an oxygen or sulphur atom, or else (ii) A and Z both represent direct bonds, and X and Y represent simultaneously ethylene and carbonyl, *trans*-vinylene and carbonyl, or ethylene and —CH(OR³)—, groups respectively (R^3 being as hereinbefore defined)] and, when R^1 represents a hydrogen atom, non-toxic salts thereof.

As will be apparent to those skilled in the art, the structure shown in general

formula I has at least two centres of chirality, these two centres of chirality being at the ring carbon atoms in positions 1 and 2, respectively. In addition to these two centres of chirality, a further centre of chirality will occur when Y represents a group —CH(OR³)—, and still further centres of chirality may occur in the groups A, R^1, R^2 and R^3. The presence of centres of chirality, as is well known, leads to the existence of isomerism. However, the compounds of formula I of the present invention all have such a configuration that the side chains attached to the ring carbon atoms in positions 1 and 2 are *trans* with respect to each other. Accordingly, all isomers of general formula I, and mixtures thereof, which have those side chains, attached to the ring carbon atoms in positions 1 and 2, in the *trans* configuration are within the scope of the present invention.

The compounds of formula I and, when R^1 represents a hydrogen atom, non-toxic salts thereof possesses valuable pharmacological properties, for example, properties typical of the related series of natural products known as prostaglandins including, for example, the production of hypotension, brochodilatation, inhibition of gastric acid secretion, healing of gastric ulcers, luteolysis, and stimulation of uterine contraction. The compounds are especially useful in the inhibition of gastric acid secretion and in the healing of gastric ulcers, and their utility is enhanced by their remarkably low activity in causing the undesired side-effect of diarrhoea.

Preferred classes of compounds of formula I according to the present invention include: —

(a) compounds of formula I wherein R^1 represents an alkyl group as hereinbefore defined, the other symbols being as hereinbefore defined;

(b) compounds of formula I wherein R^2 represents a substituted or unsubstituted heterocyclyl or aryl (other than phenyl) group or a substituted phenyl group, said substitution being as hereinbefore defined, the other symbols being as hereinbefore defined;

(c) compounds of formula I wherein *n* is 5, 7 or 8, the other symbols being as hereinbefore defined;

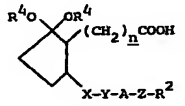
(d) compounds of formula I wherein X represents an ethylene group, the other symbols being as hereinbefore defined;

(e) compounds of formula I wherein Y represents a carbonyl group, the other symbols being as hereinbefore defined;

(f) compounds of formula I wherein A represents a direct bond, the other symbols being as hereinbefore defined; and

(g) compounds of formula I wherein Z represents an oxygen or sulphur atom, the other symbols being as hereinbefore defined.

Compounds of formula I wherein R^1 represents a hydrogen atom and Y represents a carbonyl or hydroxymethylene group, R^2, *n*, X, A and Z being as hereinbefore defined, are prepared, according to a feature of the invention, by the hydrolysis of compounds of the general formula: —



II

(wherein R^2, *n*, X, Y, A and Z are as hereinbefore defined and the symbols R^4 represent identical alkyl groups or together form an ethylene linkage unsubstituted or substituted by identical alkyl groups on each carbon atom, the symbols R^4 preferably representing together an unsubstituted ethylene linkage) by the application or adaptation of known methods for the conversion of an acetal group to a ketone group.

The hydrolysis is generally carried out in acidic conditions, for example by reaction with a dilute inorganic acid, e.g. dilute hydrochloric acid, preferably at above room temperature, e.g. between 50° and 70°C., or by means of an organic acid in the presence of water, for example aqueous acetic acid, e.g. 60—80% v/v aqueous acetic acid, or *p*-toluenesulphonic acid in acetone containing a small amount of water, preferably at temperatures between 5° and 100°C., more particularly between 15° and 30°C. Alternatively the acetal of formula II may be converted to the said ketone of formula I by subjecting it to chromatography, preferably using an eluant containing an organic acid, for example glacial acetic acid or formic acid. By this means purification is effected simultaneously with hydrolysis.

According to another feature of the invention, compounds of formula I wherein R^1 represents a hydrogen atom and Y represents a carbonyl or hydroxymethylene

group, R^2, *n*, X, A and Z being as hereinbefore defined, are converted to other compounds of formula I and to their salts by the application or adaptation of known methods of preparing salts from acids, of preparing esters from acids or alcohols, of preparing alcohols from ketones, or of reducing carbon-carbon double bonds.

For example, compounds of formula I wherein Y represents an acyloxymethylene group are prepared according to the invention by the acylation of compounds of formula I wherein Y represents a hydroxymethylene group. The acylation may be carried out, for example, by reaction with the appropriate acid anhydride, preferably in the presence of a base, e.g. pyridine, preferably at ambient temperature, optionally in the presence of an inert organic solvent such as an aromatic hydrocarbon (e.g. benzene).

Compounds of formula I wherein R^1 represents an alkyl group containing from 1 to 12 carbon atoms are prepared, according to the invention, from the corresponding acids of formula I, wherein R^1 represents a hydrogen atom, by known methods for the esterification of acids, for example by reaction of the acid with an appropriate alcohol, an excess of which may be employed as solvent medium, in the presence of an inorganic acid, e.g. hydrochloric or sulphuric acid, preferably at a temperature between 50° and 110°C. and advantageously at the reflux temperature of the reaction mixture, or with an appropriate diazoalkane in an inert organic solvent medium, preferably a dialkyl ether (e.g. diethyl ether), preferably at ambient temperature.

By the term "non-toxic salts", as used in this specification, is meant salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the parent acid compound of general formula I are not vitiated by side-effects ascribable to those cations. Preferably the salts are water-soluble. Suitable salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and pharmaceutically-acceptable (i.e. non-toxic) amine salts.

The non-toxic salts are prepared according to the invention from acids of formula I by known methods, for example by reaction of stoichiometric quantities of compounds of formula I (wherein R^1 represents a hydrogen atom) and the appropriate base, e.g. an alkali metal hydroxide or carbonate, ammonium hydroxide, ammonia or an amine, in a suitable solvent, which is preferably water in the case of the preparation of alkali metal salts and water or isopropanol in the case of amine salts. The salts may be isolated by lyophilisation of the solution or, if sufficiently insoluble in the reaction medium, by filtration, if necessary after removal of part of the solvent.

As well as being useful in themselves as pharmaceutically useful compounds, salts of the compounds of formula I wherein R^1 represents a hydrogen atom are useful for the purposes of purification of the parent acids of formula I, for example by exploitation of the solubility differences between the salts and the parent acids in water and in organic solvents, by techniques well known to those skilled in the art. The parent acids of formula I can be regenerated from their salts by known methods, for example by treatment with a mineral acid, e.g. dilute hydrochloric acid.

It is to be understood that where in this specification reference is made to compounds of formula I, it is intended to refer also, where the context so permits, to the said salts of the compounds of formula I wherein R^1 represents a hydrogen atom.

As will be readily appreciated by those skilled in the art, the isomeric forms of the compounds of the invention arising from the aforementioned centres of chirality may be separated by the application or adaptation of known methods, for example diastereoisomeric forms may be separated by chromatography using selective adsorption from solution or from the vapour phase onto suitable adsorbents.

By the term "known methods" as used in the present specification is meant methods heretofore used or described in the Chemical literature.

Compounds of formula II wherein Y represents a carbonyl or hydroxymethylene group (R^2, R^4, *n*, X, A and Z being as hereinbefore defined), but wherein X and Y do not simultaneously represent a *trans*-vinylene group and a carbonyl group respectively (hereinafter referred to as "compounds of formula IIa"), are prepared by the reduction of compounds of formula II wherein Y represents a carbonyl or hydroxymethylene group (wherein R^2, R^4, *n*, X, A and Z are as hereinbefore defined), but wherein X and Y do not simultaneously represent an ethylene group and a hydroxymethylene group respectively (hereinafter referred to as "compounds of formula IIb"). Thus: —

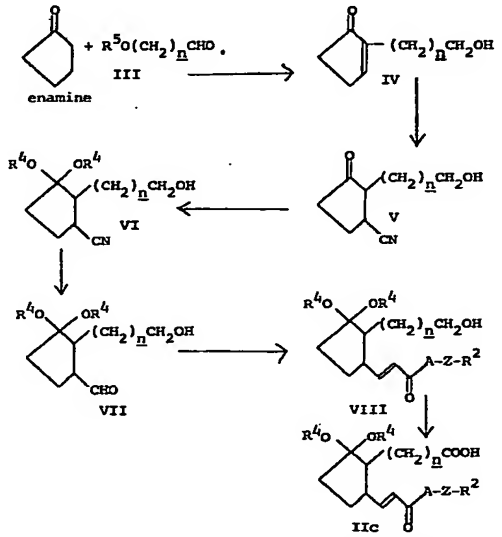
(a) Compounds of formula IIa wherein X represents an ethylene or *trans*-vinylene group and Y represents a hydroxymethylene group are prepared by reduction of the corresponding compounds of formula IIb wherein X represents an ethylene or *trans*-

vinylene group and Y represents a carbonyl group, using means and conditions capable of reducing carbonyl groups to hydroxymethylene groups without affecting carbon-carbon double bonds and carboxy groups. The reduction is preferably effected by a metal borohydride (e.g. sodium borohydride or potassium borohydride), usually in an aqueous, alcoholic or aqueous alcoholic medium and at between −40° and +30°C., preferably between −5° and +15°C., optionally in the presence of a base, for example an alkali metal hydroxide (e.g. aqueous sodium hydroxide or aqueous potassium hydroxide), or, especially when potassium borohydride is employed, in aqueous or aqueous alcoholic conditions buffered at a pH of from pH 7 to pH 9, e.g. at pH 8 (e.g. by the addition of aqueous citric acid solution). Alternatively the reduction is carried out by reaction with aluminium isopropoxide, in the presence of isopropanol, preferably as the solvent medium, at an elevated temperature, advantageously at the reflux temperature of the reaction mixture.

(b) Compounds of formula IIa wherein X represents an ethylene group and Y represents a carbonyl or hydroxymethylene group are prepared by reduction of the corresponding compounds of formula IIb wherein X represents a *trans*-vinylene group and Y represents a carbonyl or hydroxymethylene group with means and in conditions capable of reducing carbon-carbon double bonds without affecting carbonyl or carboxy groups. The reduction is preferably effected by hydrogenation in the presence of a hydrogenation catalyst, for example rhodium on charcoal or palladium on charcoal, in the presence of an inert organic solvent, for example a lower alkanol, e.g. ethanol, generally at ambient temperature and elevated pressure, e.g. at a hydrogen pressure of between 2 and 15 kilograms per square centimetre.

(c) Compounds of formula IIa wherein X represents an ethylene group and Y represents a hydroxymethylene group are prepared by reduction of corresponding compounds of formula IIb with means and in conditions capable of reducing any carbonyl groups present to hydroxymethylene groups and any *trans*-vinylene groups present to ethylene groups. The reduction is preferably effected by hydrogenation in the presence of a hydrogenation catalyst, for example Raney nickel or palladium on charcoal, in the presence of an inert organic solvent, for example a lower alkanol, e.g. ethanol, preferably at an elevated pressure, e.g. at a hydrogen pressure of between 2 and 15 kilograms per square centimetre.

Compounds of formula II wherein X represents a *trans*-vinylene group and Y represents a carbonyl group (hereinafter referred to as "compounds of formula IIc") may be prepared by the application of the following reaction sequence:—



wherein R^3 represents a hydrogen atom or an acid labile group, R^2, R^4, *n*, A and Z are as hereinbefore defined, and the double bond shown in the side-chain of formulae VIII and IIc is *trans*. Suitable acid labile groups represented by R^5 are those which are easily removed by acid hydrolysis and do not cause side reactions, e.g. the 2-tetrahydropyranyl group unsubstituted or substituted by, for example, at least one lower alkyl group.

The reaction of an aldehyde of formula III and an enamine (e.g. the morpholine enamine) of cyclopentanone to yield an alcohol of formula IV is carried out in an inert organic solvent, for example an aromatic hydrocarbon (e.g. benzene) with continuous removal of water, preferably at 60°—120°C., followed by hydrolysis in aqueous acid conditions (e.g. with hydrochloric acid), preferably at ambient temperature, and then heating with an acid, (e.g. concentrated hydrochloric acid), preferably at about 100°C., and preferably in an inert organic solvent such as an alcohol (e.g. butanol), to cause the double bond to migrate from the exocyclic to the endocyclic position.

The alcohols of general formula IV are reacted with a source of hydrogen cyanide (e.g. acetone cyanohydrin) preferably in the presence of a base, for example an alkali metal carbonate (e.g. sodium carbonate), in an aqueous organic solvent, for example an aqueous lower alkanol (e.g. aqueous methanol), preferably at 50°—110°C. and advantageously at the reflux temperature of the solvent employed, to give ketonitriles of formula V.

The acetals of general formula VI are prepared from the ketonitriles of formula V by the application or adaption of known methods for the preparation of acetals from ketones, for example by the reaction of a compound of formula V with the appropriate alcohol or diol in the presence of an acidic catalyst, for example *p*-toluenesulphonic acid, with continuous removal of water. Advantageously the reaction is effected in the presence of an inert organic solvent, for example an aromatic hydrocarbon (e.g. benzene), at an elevated temperature, with continuous removal of water by means of a Dean and Stark apparatus.

The acetals of general formula VI are reduced in an inert organic solvent, for example a lower dialkyl ether (e.g. diethyl ether), preferably at a temperature between −80°C. and +30°C., to compounds of formula VII by means of known complex metal reducing agents, preferably a dialkylaluminium hydride (e.g. diisobutylaluminium hydride) in an inert organic solvent, for example an aromatic hydrocarbon (e.g. benzene). Compounds of formula VII are described and claimed in our British Patent Specification No. 1398073.

Compounds of formula VIII are prepared by the reaction of compounds of formula VII, either with compounds of the general formula: —

$$(R^6)_3P{=}CHCO{-}A{-}Z{-}R^2 \qquad \text{IX}$$

(wherein R^2, A and Z are as hereinbefore defined, and R^6 represents an alkyl group or a phenyl group unsubstituted or substituted by an alkyl group, and advantageously represents a phenyl or *n*-butyl group), preferably in the presence of an inert organic solvent and preferably at a temperature between 20° and 100°C., for example in the presence of tetrahydrofuran as solvent at the reflux temperature of the reaction mixture or in the presence of hexamethylphosphotriamide as solvent at between 95° and 100°C., optionally under an inert atmosphere (e.g. nitrogen) or with compounds of the general formula: —

$$(R^7O)_2P(O)CH_2CO{-}A{-}Z{-}R^2 \qquad \text{X}$$

(wherein R^2, A and Z are as hereinbefore defined and R^7 represents an alkyl group of from 1 to 4 carbon atoms, preferably a methyl group), in the presence of a strong base, for example sodium hydride, preferably in the presence of an inert organic solvent, for example an ether (e.g. tetrahydrofuran), preferably at or near room temperature, and optionally under an inert atmosphere (e.g. nitrogen).

The compounds of formula VIII are then oxidised, preferably in an inert organic solvent, by means of an agent known to convert terminal hydroxymethyl to carboxy without affecting carbon-carbon double bonds or the group $-C(OR^4)_2-$ (for example chromium trioxide and sulphuric acid in dimethylformamide, preferably at a temperature of −5° to +10°C.) to give the said compounds of formula IIc.

Compounds of formula IX may be prepared by the application or adaptation of known methods, for example by the reaction between compounds of the general formula: —

$$QCH_2CO{-}A{-}Z{-}R^2 \qquad \text{XI}$$

(wherein R^2, A and Z are as hereinbefore defined and Q represents a bromine or chlorine atom) and an appropriate trialkyl or triphenyl-phosphine in a suitable organic solvent (e.g. chloroform) under a nitrogen atmosphere, preferably under anhydrous conditions and at a temperature of 20°—100°C., and advantageously at the

reflux temperature of the reaction mixture, followed by reaction of the resulting 2-oxoalkylphosphonium halide of the formula:—

$$[(R^6)_3PCH_2—CO—A—Z—R^2]^+Q^- \qquad XII$$

(wherein R^2, R^6, A, Z and Q are as hereinbefore defined) with a base (e.g. aqueous sodium carbonate or ethanolic sodium ethoxide) at ambient temperature.

Compounds of formula X may be prepared by the application or adaptation of known methods, for example by the treatment of a compound of the general formula:—

$$(R^7O)_2P(O)CH_3 \qquad XIII$$

(wherein R^7 is as hereinbefore defined) with butyl lithium at a low temperature, e.g. between −45° and −60°C., and in an inert organic solvent, e.g. a mixture of tetrahydrofuran and hexane, preferably under an inert atmosphere (e.g. nitrogen) and in anhydrous conditions, followed by treatment of the resulting mixture, containing a compound of the general formula:—

$$(R^7O)_2P(O)CH_2Li \qquad XIV$$

(wherein R^7 is as hereinbefore defined), with a compound of the general formula:—

$$R^8OOC—A—Z—R^2 \qquad XV$$

(wherein R^2, A and Z are as hereinbefore defined and R^8 represents an alkyl, preferably ethyl, group) at a temperature initially between −70° and −55°C. and subsequently rising to room temperature.

Compounds of formulae XI, XIII and XV may be prepared by the application or adaptation of known methods.

The following Examples 1 to 7 and 10 illustrate the preparation of the compounds of the present invention. Examples 8 and 9 describe the preparation of starting materials.

EXAMPLE 1

(i) 7-[5-(3-Oxoalk-*trans*-1-enyl)-2-oxocyclopentyl]heptanoic acids

A mixture of 7-{1,4-dioxa-7-(3-oxo-5-phenylpent-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid [1.0 g; prepared as described hereinafter in Example 1(ii)] and hydrochloric acid (2N; 20 ml.) was stirred at 60—65°C. for 2 hours and then extracted with diethyl ether. The ethereal solution was extracted with aqueous sodium carbonate solution (2N) and the resulting aqueous extract was acidified to pH 1 by the addition of dilute hydrochloric acid (2N), was saturated with sodium chloride, and extracted with diethyl ether. This ethereal extract was washed with water, dried over anhydrous magnesium sulphate and the diethyl ether was evaporated off. The resulting residue was purified by preparative thin layer chromatography on silica gel using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as eluant, to give 7-[5-(3-oxo-5-phenylpent-*trans*-1-enyl)-2-oxocyclopentyl]heptanoic acid (0.5 g.) in the form of a pale yellow oil.

[Elemental analysis: C, 74.5; H, 8.6%; $C_{23}H_{30}O_4$ requires: C, 74.6; H, 8.2%. ν_{max} 990 cm^{-1}, 1625 cm^{-1}, 1670 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1}. The nuclear magnetic resonance spectrum (N.M.R.) of a 10% solution in deuterochloroform displayed the following peaks:— multiplets at 7.26δ, 2.94δ, 2.0—2.6δ, 1.0—2.0δ, doublet of doublets at 6.78δ (J=15.5 and 7.5 cycles/second), doublet at 6.15δ, singlet at 10.5δ].

By proceeding in a similar manner, but substituting for the 7-{1,4-dioxa-7-(3-oxo-5-phenylpent-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid used as starting material the appropriate quantities of

7-{1,4-dioxa-7-(3-oxo-4-phenylbut-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid,

7-{1,4-dioxa-7-(3-oxo-3-phenylprop-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid,

7-{1,4-dioxa-7-(3-oxo-6-phenylhex-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid,

7-{1,4-dioxa-7-(3-oxo-4-phenylhept-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid,

7-{1,4-dioxa-7-(3-oxo-4-phenyloct-*trans*-1-enyl)spiro[4,4]non-6-yl}heptanoic acid,

7 - {1,4 - dioxa - 7 - (4 - benzyl - 3 - oxooct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid,

7 - {1,4 - dioxa - 7 - (4 - *p* - chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid,

7 - {1,4 - dioxa - 7 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}hexanoic acid,

7 - {1,4 - dioxa - 7 - (3 - *p* - bromophenyl - oxoprop - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid, and

7 - {1,4 - dioxa - 7 - (3 - oxo - 3 - thien - 2' - ylprop - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid,

all prepared as described hereinafter in Example 1(ii), there were prepared

7 - [5 - (3 - oxo - 4 - phenylbut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 73.7; H, 8.2%; $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%. ν_{max} 985 cm^{-1}, 1620 cm^{-1}, 1665 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1}. N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.3δ, singlet at 3.88δ, doublet at 6.23δ (J=15.5 cycles/second), doublet of doublets at 6.9δ (J=15.5 and 7.5 cycles/second), multiplets at 7.3δ and 1.0—2.9δ],

7 - [5 - (3 - oxo - 3 - phenylprop - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 73.7; H, 7.8%; $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.65%. ν_{max} 995 cm^{-1}, 1620 cm^{-1}, 1690 cm^{-1}, 1700 cm^{-1}, 1720 cm^{-1}, 1730 cm^{-1}. N.M.R. (approximately 10% w/v solution in deuterochloroform): multiplets at 7.8—8.2δ, 7.35—7.8δ, 6.8—7.3δ and 1.9—3.0δ. λ_{max} 259 mμ ε_{max} 15500],

7 - [5 - (3 - oxo - 6 - phenylhex - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid,

[Elemental analysis: C, 75.3; H, 8.5%; $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%. ν_{max} 990 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1}. N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.5δ, doublet at 6.18δ (J=16 cycles/second), doublet of doublets at 6.76δ (J=8 and 16 cycles/second), multiplets at 7.24δ and 1.0—2.9δ],

7 - [5 - (3 - oxo - 4 - phenylhept - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 75.4; H, 8.9%; $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%. ν_{max} 995 cm^{-1}, 1630 cm^{-1}, 1665 cm^{-1}, 1705 cm^{-1}, 1725 cm^{-1}. N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.2δ, singlet at 7.2δ, doublet at 6.1δ (J=15.5 cycles/second), doublet of doublets at 6.8δ (J=15.5 and 7 cycles/second), multiplets at 3.8δ, 1.0—2.6δ and 0.9δ],

7 - [5 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 76.1; H, 9.1%; $C_{26}H_{36}O_4$ requires C, 75.7; H, 8.8%. ν_{max} 980 cm^{-1}, 1615 cm^{-1}, 1655 cm^{-1}, 1695 cm^{-1}, 1725 cm^{-1}. N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 9.6δ, doublet at 6.15δ (J=15.5 cycles/second), doublet of doublets at 6.8δ (J=15.5 and 7.5 cycles/second) and 3.77δ (J=7 cycles/second), triplets at 2.31δ and 0.85δ, multiplets at 7.1—7.4δ, 1.05—2.8δ],

7 - [5 - (4 - benzyl - 3 - oxooct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid

[Elemental analysis: C, 76.4; H, 9.0%; $C_{27}H_{38}O_4$ requires C, 76.0; H, 9.0%. ν_{max} 990 cm^{-1}, 1625 cm^{-1}, 1660 cm^{-1}, 1705 cm^{-1}, 1730 cm^{-1}. N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.8δ, doublet at 6.12δ (J=16 cycles/second), doublet of doublets at 6.67δ (J=7 and 16 cycles/second), triplet at 0.88δ, multiplets at 7.18δ, 2.6—3.2δ, 2.0—2.6δ, 1.5—2.0δ],

7 - [5 - (4 - *p* - chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 70.2; H, 8.4%; $C_{27}H_{37}ClO_4$ requires: C, 70.3; H, 8.1%. ν_{max} 990 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1}, N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 9.8δ, doublet at 6.14δ (J=16 cycles/second), doublet of doublets at 6.7δ (J=16 and 8 cycles/second), triplet at 0.86δ, multiplets at 6.9—7.35δ, 2.6—3.2δ, 1.05—2.6δ],

7 - [5 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 76.2; H, 9.5%; $C_{28}H_{40}O_4$ requires C, 76.3; H, 9.7%. ν_{max} 990 cm^{-1}, 1625 cm^{-1}, 1660 cm^{-1}, 1705 cm^{-1}, 1730 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 9.43δ, doublet at 6.13δ (J=15.5 cycles/second), doublet of doublets at 6.68δ (J=15.5 and 7 cycles/second), triplet at 0.88δ multiplets at 7.03δ, 2.6—3.2δ, 2.3δ, 2.1—2.6δ, 1.05—2.1δ],

7 - [5 - (3 - *p* - bromophenyl - 3 - oxoprop - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid

[Elemental analysis: C, 60.1; H, 6.5%; $C_{21}H_{25}BrO_4$ requires: C, 59.9; H, 6.5%. ν_{max} 990 cm^{-1}, 1070 cm^{-1}, 1615 cm^{-1}, 1665 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.65δ, multiplets at 7.88δ, 7.65δ, 6.8—7.2δ, 2.0—2.9δ, 1.0—2.0δ], and

7 - [5 - (3 - oxo - 3 - thien - 2′ - ylprop - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

[Elemental analysis: C, 65.3; H, 7.2%; $C_{19}H_{24}O_4S$ requires C, 65.5; H, 6.9%. ν_{max} 985 cm^{-1}, 1415 cm^{-1}, 1515 cm^{-1}, 1605 cm^{-1}, 1645 cm^{-1}, 1690 cm^{-1}, 1720 cm^{-1}, λ_{max} 298 mμ, ε_{max} 11,600; λ_{max} 271 mμ, ε_{max} 11,100.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 9.3δ, multiplets at 7.6—7.9δ, 6.7—7.35δ, 1.9—3.0δ and 1.0—1.9δ] respectively.

(ii) 7 - {1,4 - Dioxa - 7 - (3 - oxoalk - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}-heptanoic acids

Anhydrous chromium trioxide (4.4 g.) was added portionwise with stirring to a solution of 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane [3.85 g; prepared as described hereinafter in Example 1 (iii)] in anhydrous dimethylformamide (60 ml.) at a temperature below 10°C. A solution of concentrated sulphuric acid (1.4 ml.) in dimethylformamide (60 ml.) was added and the mixture was stirred at below 10°C. for 1 hour. Diethyl ether (200 ml.) was then added followed by water (100 ml.), and the ethereal layer was separated and then extracted with aqueous sodium carbonate solution (2N). The resulting aqueous solution was acidified to pH 4 by the addition of dilute hydrochloric acid (2N) and then saturated with sodium chloride and extracted with diethyl ether. The resulting ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated, to give 7 - {1,4 - dioxa - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl)-spiro[4,4]non - 6 - yl}heptanoic acid (2.0 g.), in the form of a yellow oil. (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1665 cm^{-1}, 1700 cm^{-1}). This material was used for the next stage without further purification being necessary.

By proceeding in a similar manner, but substituting for the 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane used as starting material the appropriate quantities of

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenylbut - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 3 - phenylprop - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 6 - phenylhex - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenylhept - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (4 - benzyl - 3 - oxooct - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (4 - *p* - chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

6 - (7 - hydroxyheptyl) - 7 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane,

7 - (3 - *p* - bromophenyl - 3 - oxoprop - *trans* - 1 - enyl) - 6 - (7 - hydroxyheptyl) - 1,4 - dioxaspiro[4,4]nonane, and

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 3 - thien - 2′ - ylprop - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane [all prepared as hereinafter described in Example 1 (iii)], there were prepared

7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenylbut - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl} - heptanoic acid (ν_{max} 950 cm^{-1}, 985 cm^{-1}, 1625 cm^{-1}, 1675 cm^{-1}, 1710 cm^{-1}),

7 - {1,4 - dioxa - 7 - (3 - oxo - 3 - phenylprop - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 960 cm^{-1}, 995 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 1700 cm^{-1}),

7 - {1, 4- dioxa - 7 - (3 - oxo - 6 - phenylhex - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 995 cm^{-1}, 990 cm^{-1}, 1625 cm^{-1}, 1670 cm^{-1}, 1700 cm^{-1}),

7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenylhept - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 955 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 1700 cm^{-1}),

7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 955 cm^{-1}, 995 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1690 cm^{-1}, 1705 cm^{-1}),

7 - {1,4 - dioxa - 7 - (4 - benzyl - 3 - oxooct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 1705 cm^{-1}),

7 - {1,4 - dioxa - 7 - (4 - *p* - chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 985 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1710 cm^{-1}),

7 - {1,4 - dioxa - 7 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 1705 cm^{-1}),

7 - {1,4 - dioxa - 7 - (3 - *p* - bromophenyl - 3 - oxoprop - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1070 cm^{-1}, 1620 cm^{-1}, 1665 cm^{-1}, 1705 cm^{-1}) and

7 - {1,4 - dioxa - 7 - (3 - oxo - 3 - thien - 2′ - ylprop - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1415 cm^{-1}, 1515 cm^{-1}, 1605 cm^{-1}, 1645 cm^{-1}, 1695 cm^{-1}), respectively.

(iii) 6 - (7 - Hydroxyheptyl) - 7 - (3 - oxoalk - *trans* - 1 - enyl) - 1,4 - dioxaspiro-[4,4]nonanes

(a) A solution of dimethyl 2 - oxo - 4 - phenylbutylphosphonate (2.5 g; prepared as described hereinafter in Example 9) in anhydrous tetrahydrofuran (50 ml.) was added to a stirred suspension of sodium hydride (0.24 g.) in tetrahydrofuran (20 ml.). The mixture was stirred at room temperature in an atmosphere of nitrogen for 24 hours, then treated dropwise with a solution of 7 - formyl- 6 - (7 - hydroxyheptyl) - 1,4 - dioxaspiro[4,4]nonane [2.7 g; prepared as described in our British Patent Specification No. 1398073] in tetrahydrofuran (30 ml.) and stirred for a further 2 hours in an atmosphere of nitrogen. The mixture was acidified to pH 4 by the addition of glacial acetic acid, the solvents were removed *in vacuo* and the residue was extracted with diethyl ether. The ethereal solution was washed with aqueous sodium bicarbonate solution (10% w/v) and then with water and dried over anhydrous magnesium sulphate. Evaporation of the solution gave 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (3.9 g.), in the form of a yellow oil (ν_{max} 955 cm^{-1}, 990 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1690 cm^{-1}).

By proceeding in a similar manner, but substituting the appropriate quantity of dimethyl 2 - oxo - 3 - phenylpropylphosphonate (prepared as hereinafter described in Example 9) for the dimethyl 2 - oxo - 4 - phenyltbutylphosphonate used as a starting material, there was prepared 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenylbut - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 955 cm^{-1}, 990 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1685 cm^{-1}).

(b) A mixture of 7 - formyl - 6 - (7 - hydroxyheptyl) - 1,4 - dioxaspiro[4,4]-nonane (4.0 g.) and benzoylmethylenetriphenylphosphorane (5.6 g; prepared according to the method of F. Ramirez and S. Dershowitz, J. Org. Chem. 1957, *22*, 41) in hexamethylphosphotriamide (35 ml.) was heated on a steam bath under dry nitrogen for 48 hours then poured into water (200 ml.). The mixture was extracted with diethyl ether and the ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated. The residue was triturated with a mixture of petroleum ether (b.p. 40—60°C.) and diethyl ether, allowed to stand at 0°C, then filtered to remove triphenylphosphine oxide. The filtrate was evaporated to give 6 - (7 - hydroxyheptyl) - 7 - (3 - phenyl - 3 - oxoprop - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 985 cm^{-1}, 1615 cm^{-1}, 1660 cm^{-1}, 3380 cm^{-1}).

By proceeding in a similar manner, but substituting the appropriate quantity of

5 - phenyl - 2 - oxopentylidenetriphenylphosphorane [prepared as hereinafter described in Example 8 (i)] for the benzoylmethylenetriphenylphosphorane used as a starting material, there was prepared 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 6 - phenylhex - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1680 cm^{-1}, 3335 cm^{-1}).

By again proceeding in a similar manner but substituting for the benzoylmethylenetriphenylphosphorane used as starting material the appropriate quantities of

3 - phenyl - 2 - oxohexylidenetriphenylphosphorane,
3 - phenyl - 2 - oxoheptylidenetriphenylphosphorane,
3 - benzyl - 2 - oxoheptylidenetriphenylphosphorane,
3 - *p* - chlorobenzyl - 2 - oxoheptylidenetriphenylphosphorane,
3 - *p* - methylbenzyl - 2 - oxoheptylidenetriphenylphosphorane [these last-named five compounds being prepared as hereinafter described in Example 8(i)],
p - bromobenzoylmethylenetriphenylphosphorane (prepared according to the method of A. V. Dombrovskii and M. I. Shevchuk, Zh. Obshch. Khim. 1963, *33*, 1263, Chem. Abstr. 1963, *59*, 10113b) and

then - 2 - oylmethylenetriphenylphosphorane [prepared according to the method of A. V. Dombrovskii, M. I. Shevchuk and A. A. Grigorenko, Metody Poluch. Khim. Reaktivov Prep. 1966, No. 14, 147 (Chem. Abstr. 1967, *67*, 43889x), there were prepared:—

6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenylhept - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1625 cm^{-1}, 1690 cm^{-1}, 3400 cm^{-1});
6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 980 cm^{-1}, 1615 cm^{-1}, 1675 cm^{-1}, 3335 cm^{-1}),
7 - (4 - benzyl - 3 - oxooct - *trans* - 1 - enyl) - 6 - (7 - hydroxyheptyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 3400 cm^{-1}),
7 - (4 - *p* - chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl) - 6 - (7 - hydroxyheptyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 955 cm^{-1}, 995 cm^{-1}, 1615 cm^{-1}, 1680 cm^{-1}, 3335 cm^{-1}),
6 - (7 - hydroxyheptyl) - 7 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 955 cm^{-1}, 990 cm^{-1}, 1625 cm^{-1}, 1685 cm^{-1}, 3400 cm^{-1}),
7 - (3 - *p* - bromophenyl - 3 - oxoprop - *trans* - 1 - enyl) - 6 - (7 - hydroxyheptyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1070 cm^{-1}, 1615 cm^{-1}, 1665 cm^{-1}, 3400 cm^{-1}), and
6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 3 - thien - 2′ - ylprop - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 960 cm^{-1}, 995 cm^{-1}, 1245 cm^{-1}, 1525 cm^{-1}, 1610 cm^{-1}, 1655 cm^{-1}, 3335 cm^{-1}), respectively.

EXAMPLE 2

(i) 7 - {5 - [4 - (2 - Phenylethyl) - 3 - oxooct - *trans* - 1 - enyl] - 2 - oxocyclopentyl} - heptanoic acid.

A solution of 7 - {1,4 - dioxa - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl]spiro[4,4]non - 6 - yl}heptanoic acid [0.4 g; prepared as described hereinafter in Example 2(ii)] in acetic acid (10 ml.) and water (5 ml.) was kept at room temperature for 4 hours then evaporated *in vacuo* at a temperature below 50°C. The residue was dissolved in diethyl ether and the ethereal solution was washed with water and then extracted with aqueous sodium carbonate solution (2N). This aqueous solution was then acidified to pH 3 by the addition of dilute hydrochloric acid (2N), saturated with sodium chloride, and extracted with diethyl ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by preparative thin layer chromatography on silica gel using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as eluant, to give 7 - {5 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid (0.12 g),

[Elemental analysis: C, 76.1; H, 9.5%; $C_{28}H_{40}O_4$ requires: C, 76.3; H, 9.2%. ν_{max} 995 cm^{-1}, 1630 cm^{-1}, 1665 cm^{-1}, 1710 cm^{-1}, 1735 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.5δ, singlet at 7.25δ, doublet at 6.2δ (J=16 cycles/second), doublet of doublets at 6.8δ (J=16 and 7.5 cycles/second), triplet at 0.87δ, multiplets at 1.05—3.0δ].

(ii) 7 - {1,4 - Dioxa - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl]spiro-[4,4]non - 6 - yl}heptanoic acid

By proceeding in a similar manner to that described above in Example 1(ii), but replacing the 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane used as starting material by the appropriate quantity of 6 - (7 - hydroxyheptyl) - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl] - 1,4 - dioxaspiro[4,4]nonane [prepared as hereinafter described in Example 2(iii)], there was prepared 7 - {1,4 - dioxa - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl]spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1625 cm^{-1}, 1660 cm^{-1}, 1710 cm^{-1}).

(iii) 6 - (7 - Hydroxyheptyl) - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl] - 1,4 - dioxaspiro[4,4]nonane

By proceeding in a similar manner to that described above in Example 1(iii)(a), but replacing the dimethyl 2 - oxo - 4 - phenylbutylphosphonate used as starting material by the appropriate quantity of dimethyl 2 - oxo - 3 - (2 - phenylethyl)-heptylphosphonate (prepared as hereinafter described in Example 9), there was prepared 6 - (7 - hydroxyheptyl) - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl] - 1,4 - dioxaspiro[4,4]nonane (ν_{max} 950 cm^{-1}, 990 cm^{-1}, 1620 cm^{-1}, 1655 cm^{-1}, 1680 cm^{-1}).

EXAMPLE 3

(i) 7 - [5 - (3 - Hydroxyalk - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acids

By proceeding in a similar manner to that described in Example 1(i) for the preparation of 7 - [5 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid, but substituting for the 7 - {1,4 - dioxa - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid, used as starting material, the appropriate quantities of 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 4 - phenyloct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl} - heptanoic acid, 7 - {1,4 - dioxa - 7 - (4 - *p* - chlorobenzyl - 3 - hydroxyoct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid and 7 - {1,4 - dioxa - 7 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid [all three prepared as hereinafter described in Example 3(ii)], there were prepared

7 - [5 - (3 - hydroxy - 4 - phenyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid,

[Elemental analysis: C, 75.2; H, 9.5%; $C_{26}H_{38}O_4$ requires: C, 75.3; H, 9.2%; ν_{max} 980 cm^{-1}, 1705 cm^{-1}, 1730 cm^{-1}, 3450 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 6.7δ, triplet at 0.81δ (J=6 cycles/second), multiplets at 6.9—7.4δ, 5.25—5.7δ, 4.2δ, 2.0—2.6δ, 1.0—2.0δ],

7 - [5 - (4 - *p* - chlorobenzyl - 3 - hydroxyoct - *trans* - 1 - enyl) - 2 - oxocyclo-pentyl]heptanoic acid,

[Elemental analysis: C, 69.7; H, 8.8%; $C_{27}H_{39}ClO_4$ requires: C, 70.0; H, 8.5%. ν_{max} 975 cm^{-1}, 1700 cm^{-1}, 1725 cm^{-1}, 3400 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): multiplets at 7.0—7.3δ, 5.4—5.7δ, 4.1δ, 1.0—2.05δ and 0.87δ] and

7 - [5 - (4 - *p* - methylbenzyl - 3 - hydroxyoct - *trans* - 1 - enyl) - 2 - oxo-cyclopentyl]heptanoic acid,

[Elemental analysis: C, 76.0; H, 9.6%; $C_{28}H_{42}O_4$ requires C, 76.0; H, 9.6%. ν_{max} 975 cm^{-1}, 1705 cm^{-1}, 1730 cm^{-1}, 3450 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlets at 6.45δ, 2.3δ, triplet at 0.88δ, multiplets at 7.1δ, 5.55—5.75δ, 4.15δ, 2.0—2.9δ, and 1.1—2.0δ], respectively.

(ii) 7 - {1,4 - Dioxa - 7 - (3 - hydroxyalk - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}-heptanoic acids

A solution of 7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl)-spiro[4,4]non - 6 - yl}heptanoic acid [0.8 g; prepared as hereinbefore described in Example 1(ii)] in methanol (12 ml.) was added to aqueous sodium citrate solution (160 ml; 2% w/v) and cooled to −5°C. Potassium borohydride (2.4 g.) was added portionwise with stirring over a period of 30 minutes, keeping the temperature at −5°C. and maintaining the pH at pH 8 by means of the addition of small quantities of aqueous citric acid solution (10% w/v). The solution was stirred for 2 hours at −5° to 0°C. at pH 8, acetone (24 ml.) was added, and then a further quantity of the aqueous citric acid solution was added until the solution had reached pH 4. The mixture was saturated with sodium chloride and extracted with diethyl ether. The

ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated, to give 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 4 - phenyloct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (0.8 g.), in the form of a yellow oil. (ν_{max} 955 cm^{-1}, 975 cm^{-1}, 1705 cm^{-1}, 3440 cm^{-1}). By proceeding in a similar manner but substituting for the 7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl)-spiro[4,4]non - 6 - yl}heptanoic acid used as starting material the appropriate quantities of 7 - {1,4 - dioxa - 7 - (4 - *p* - chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid and 7 - {1,4 - dioxa - 7 - (4 - *p* - methylbenzyl - 3 - oxooct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid [both prepared as hereinbefore described in Example 1(ii)], there were prepared 7 - {1,4 - dioxa - 7 - (4 - *p* - chlorobenzyl - 3 - hydroxyoct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}; 975 cm^{-1}; 1705 cm^{-1}; 3400 cm^{-1}) and 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 4 - *p* - methylbenzyloct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}; 975 cm^{-1}; 1700 cm^{-1}; 3400 cm^{-1}), respectively.

EXAMPLE 4

(i) 7 - {5 - [3 - hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid

A solution of 7 - {1,4 - dioxa - 7 - [3 - hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl]spiro[4,4]non - 6 - yl}heptanoic acid [0.77 g; prepared as hereinafter described in Example 4(ii)] in acetic acid (16 ml.) and water (8 ml.) was kept at room temperature for 4 hours then evaporated *in vacuo* at a temperature below 50°C. The residue was dissolved in diethyl ether and the ethereal solution was washed with water and then extracted with aqueous sodium carbonate solution (2N). This solution was acidified to pH 3 by the addition of dilute hydrochloric acid (2N), and then saturated with sodium chloride and extracted with diethyl ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated, to give crude 7 - {5 - [3 - hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid (0.6 g.) as a mixture of diastereoisomers.

The mixture was purified and partially separated by preparative thin-layer chromatography, on silica gel, using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as eluant to produce two distinct diastereoisomeric components. By analogy with known prostaglandins the material (0.13 g.) farther from the origin ("component 4a") was thought to be a 1:1:1:1 mixture of the isomers

and their enantiomers.

[Elemental analysis: C, 76.1; H, 9.8%; $C_{28}H_{42}O_4$ requires C, 76.0; H, 9.6%. ν_{max} 975 cm^{-1}, 1700 cm^{-1}, 1725 cm^{-1}, 3450 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlets at 7.23δ, 6.48, triplets at 2.67δ, 2.30δ, 0.90δ and multiplets at 5.55—5.78, 4.19δ, 1.05—2.78].

Similarly the material (0.07 g.) nearer the origin ("component 4b") was thought to be a 1:1:1:1 mixture of the isomers

and their enantiomers.

[Elemental analysis: C, 75.7; H, 9.8%].

As is conventional, the symbol - - - signifies a bond below the plane of the diagram and signifies a bond above the plane of the diagram. The infra-red and N.M.R. spectra of component 4b were virtually identical with those displayed by component 4a.

(ii) 7 - {1,4 - Dioxa - 7 - [3 - hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl]-spiro[4,4]non - 6 - yl}heptanoic acid

By proceeding in a similar manner to that described above in Example 3(ii) for

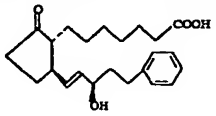
the preparation of 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 4 - phenyloct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid, but replacing the 7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenyloct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid used as starting material by the appropriate quantity of 7 - {1,4 - dioxa - 7 - [4 - (2 - phenylethyl) - 3 - oxooct - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid [prepared as hereinbefore described in Example 2(ii)], there was prepared 7 - {1,4 - dioxa - 7 - [3 - hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl]spiro[4,4]non - 6 - yl}heptanoic acid (ν_{max} 955 cm^{-1}, 980 cm^{-1}, 1710 cm^{-1}, 3450 cm^{-1}).

EXAMPLE 5

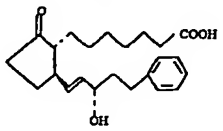
(i) 7 - [5 - (3 - Hydroxy - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid

A solution of 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 5 - phenylpent - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid [1.0 g; prepared as hereinafter described in Example 5(ii)] in acetic acid (10 ml.) and water (5 ml.) was kept at room temperature for 4 hours and then evaporated *in vacuo* at a temperature below 50°C. The residue was dissolved in diethyl ether and the ethereal solution was washed with water then extracted with aqueous sodium carbonate solution (2N). This solution was acidified to pH 3 by the addition of dilute hydrochloric acid (2N), and then saturated with sodium chloride and extracted with diethyl ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated, to give crude 7 - [5 - (3 - hydroxy - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid (0.8 g.) (ν_{max} 975 cm^{-1}, 1700 cm^{-1}, 1720 cm^{-1}) as a mixture of diastereoisomers, in the form of an oil. The mixture was purified and partially separated into diastereoisomeric components by preparative thin layer chromatography on silica gel using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as eluant, eluting the plates twice each

By analogy with known prostaglandins the material (126 mg.) farther from the origin ("component 5a") was thought to be a 1:1 mixture of the isomer



and its enantiomer, while the material (112 mg.) nearer to the origin ("component 5b") was thought to be a 1:1 mixture of the isomer



and its enantiomer.

(ii) 7 - {1,4 - Dioxa - 7 - (3 - hydroxy - 5 - phenylpent - *trans* - 1 - enyl)spiro[4,4]-non - 6 - yl}heptanoic acid

A solution of 7 - {1,4 - dioxa - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl)-spiro[4,4]non - 6 - yl}heptanoic acid [1.0 g; prepared as hereinbefore described in Example 1(ii)] in methanol (10 ml.) was added to aqueous sodium citrate solution (160 ml; 2% w/v) and cooled to −5°C. Potassium borohydride (3.2 g.) was added, portionwise with stirring over a period of 30 minutes, keeping the temperature at −5°C. and the pH at pH 8 by means of the addition of small quantities of aqueous citric acid solution (10% w/v). The solution was stirred for 2 hours at −5° to 0°C. at pH 8, acetone (25 ml.) was added, and then a further quantity of the aqueous citric acid solution was added until the solution had reached pH 4. The mixture was saturated with sodium chloride and extracted with diethyl ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated to give 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 5 - phenylpent - *trans* - 1 - enyl)spiro[4,4]-non - 6 - yl}heptanoic acid (0.8 g.) in the form of a yellow oil (ν_{max} 955 cm^{-1}, 975 cm^{-1}, 1700 cm^{-1}, 3400 cm^{-1}).

EXAMPLE 6

7 - [5 - (3 - Hydroxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid

(i) Preparation of 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 3 - phenylpropyl)spiro[4,4]-non - 6 - yl}heptanoic acid.

A solution of 7 - {1,4 - dioxa - 7 - (3 - phenyl - 3 - oxoprop - *trans* - 1 -

enyl)spiro[4,4]non - 6 - yl}heptanoic acid [1.0 g; prepared as described hereinbefore in Example 1(ii)] in ethanol (50 ml.) and a palladium charcoal catalyst (0.25 g.) were shaken together with hydrogen (2.8 kg/cm²) for 1 hour at 25°C. The catalyst was filtered off and evaporation of the solvent gave 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 3 - phenylpropyl)spiro[4,4]non - 6 - yl}heptanoic acid (0.95 g.), (ν_{max} 955 cm^{-1}, 1705 cm^{-1}, 1715 cm^{-1}, 3450 cm^{-1}).

This material was used for the next step, the preparation of 7 - [5 - (3 - hydroxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid, without further purification being necessary.

(ii) Preparation of 7 - [5 - (3 - hydroxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]-heptanoic acid

A solution of 7 - {1,4 - dioxa - 7 - (3 - hydroxy - 3 - phenylpropyl)spiro[4,4]-non - 6 - yl}heptanoic acid (0.5 g.) in acetic acid (10 ml.) and water (5 ml.) was kept at 25°C. for 4 hours and then evaporated *in vacuo* at below 50°C.

The residue was dissolved in diethyl ether and the ethereal solution was washed with water, dried over anhydrous magnesium sulphate, and evaporated. The residue was purified, by preparative thin-layer chromatography on silica gel using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as eluant, to give 7 - [5 - (3 - hydroxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid (0.2 g.), in the form of an almost colourless oil.

[Elemental analysis: C, 73.0; H, 8.7%; $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%. ν_{max} 1705 cm^{-1}, 1730 cm^{-1}, 3450 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlet at 7.35δ, multiplets at 4.67δ and 1.0—2.45δ].

EXAMPLE 7

Acetates

A solution of 7 - [5 - (3 - hydroxy - 4 - *p* - methylbenzyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid [0.335 g; prepared as described hereinbefore in Example 3(i)] in anhydrous pyridine (10 ml.) and acetic anhydride (10 ml.) was kept at 25°C. for 43 hours and then poured into a mixture of ice and water (about 30 ml.). The resulting mixture was extracted with diethyl ether and the ethereal extracts were washed with dilute hydrochloric acid (2N), then with water, and dried over anhydrous magnesium sulphate. The solution was evaporated and the residue was purified, by preparative thin layer chromatography on silica gel using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as eluant, to give 7 - [5 - (3 - acetoxy - 4 - *p* - methylbenzyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid (0.18 g.), in the form of a yellow oil.

[Elemental analysis: C, 74.5; H, 9.5%; $C_{30}H_{44}O_5$ requires: C, 74.3; H, 9.15%. ν_{max} 1240 cm^{-1}, 1710 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.6δ, singlets at 7.08δ, 2.33δ, 2.04δ, triplet at 0.87δ, multiplets at 5.2—5.8δ, 2.0—2.8δ and 1.05—2.0δ].

By proceeding in a similar manner, but substituting the appropriate quantity of 7 - [5 - (3 - hydroxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid (prepared as hereinbefore described in Example 6) for the 7 - [5 - (3 - hydroxy - 4 - *p* - methylbenzyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid used as starting material, there was prepared 7 - [5 - (3 - acetoxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid.

[Elemental analysis: C, 71.5, H, 8.6%; $C_{28}H_{32}O_5$ requires: C, 71.1; H, 8.3%. ν_{max} 1240 cm^{-1}, 1705 cm^{-1}, 1725 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): broad singlet at 10.25δ, singlet at 2.10δ, multiplets at 7.37δ, 5.78δ, 2.0—2.6δ, 1.0—2.0δ].

By again proceeding in a similar manner, but substituting the appropriate quantity of 7 - {5 - [3 - hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid [crude mixture of diastereoisomers, prepared as hereinbefore described in Example 4(i)] for the 7 - [5 - (3 - hydroxy - 4 - *p* - methylbenzyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid used as starting material, there was prepared 7 - {5 - [3 - acetoxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid,

[Elemental analysis: C, 74.2; H, 9.4%; $C_{30}H_{44}O_5$ requires: C, 74.3; H, 9.2%. ν_{max} 1235 cm^{-1}, 1700 cm^{-1}, 1710 cm^{-1}].

EXAMPLE 8

Acylmethylenetriphenylphosphoranes

(i) Preparation of acylmethylenetriphenylphosphoranes

(a) A solution of sodium (0.1 g.) in anhydrous ethanol (3.8 ml.) was added to a solution of 5 - phenyl - 2 - oxopentyltriphenylphosphonium chloride [1.0 g; prepared as hereinafter described in Example 8(ii)] in anhydrous ethanol (10 ml.) and the resulting mixture was left to stand at room temperature for 4 hours. The mixture was concentrated to half its bulk by removal of ethanol *in vacuo* and then diluted with water (50 ml.) and extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulphate and evaporated to dryness. The residual oil was triturated with light petroleum ether (b.p. 40—60°C.) and then recrystallised from cyclohexane, to give 5 - phenyl - 2 - oxopentylidenetriphenylphosphorane (0.6 g.), in the form of a white crystalline solid, m.p. 93—95°C.

[Elemental analysis: C, 82.8; H, 6.5; P, 7.6%; $C_{29}H_{27}OP$ requires: C, 82.4; H, 6.4; P, 7.3%. ν_{max} 1100 cm^{-1}, 1400 cm^{-1}, 1440 cm^{-1}, 1485 cm^{-1}, 1540 cm^{-1}).

(b) 3 - Phenyl - 2 - oxoheptyltriphenylphosphonium chloride [7.9 g; prepared as hereinafter described in Example 8 (ii)] was added to a stirred aqueous solution of sodium carbonate (80 ml; 10% w/v) at room temperature. The mixture was stirred for 5 hours and then extracted with diethyl ether. The ethereal solution was washed with water, dried over anhydrous magnesium sulphate and evaporated, to give a yellow oil from which a white solid was obtained upon trituration with light petroleum ether (b.p. 40—60°C.). Recrystallisation of this material from light petroleum ether (b.p. 60—80°C.) gave 3 - phenyl - 2 - oxoheptylidenetriphenylphosphorane (4.0 g.), in the form of colourless prisms, m.p. 89—91°C.

[Elemental analysis: C, 83.0; H, 6.9; P, 7.0%; $C_{31}H_{31}OP$ requires: C, 82.6; H, 6.9; P, 6.9%. ν_{max} 1100 cm^{-1}, 1380 cm^{-1}, 1435 cm^{-1}, 1480 cm^{-1}, 1450 cm^{-1}).

By proceeding in a similar manner, but using the appropriate acylmethyltriphenylphosphonium chlorides [all prepared as described hereinafter in Example 8(ii)] as starting materials, there were prepared

3 - phenyl - 2 - oxohexylidenetriphenylphosphorane (ν_{max} 1105 cm^{-1}, 1485 cm^{-1}, 1440 cm^{-}, 1485 cm^{-1}, 1550 cm^{-1}),

3 - benzyl - 2 - oxoheptylidenetriphenylphosphorane (ν_{max} 1110 cm^{-1}, 1395 cm^{-1}, 1440 cm^{-1}, 1485 cm^{-1}, 1545 cm^{-1}),

3 - *p* - chlorobenzyl - 2 - oxoheptylidenetriphenylphosphorane (ν_{max} 1110 cm^{-1}, 1395 cm^{-1}, 1445 cm^{-1}, 1485 cm^{-1}, 1550 cm^{-1}), and

2 - *p* - methylbenzyl - 2 - oxoheptylidenetriphenylphosphorane, m.p. 111—115°C.

[Elemental analysis: C, 82.7; H, 7.4; P, 6.7%; $C_{35}H_{35}OP$ requires: C, 82.8; H, 7.4; P, 6.5%. ν_{max} 1110 cm^{-1}, 1395 cm^{-1}, 1440 cm^{-1}, 1485 cm^{-1} 1545 cm^{-1}), respectively.

(ii) Preparation of acylmethyltriphenylphosphonium chlorides

A solution of 1 - chloro - 5 - phenylpentan - 2 - one; [6.55 g; prepared as hereinafter described in Example 8(iii)] in dry chloroform (30 ml.) was added to a solution of triphenylphosphine (8.7 g.) in dry chloroform (30 ml.) and heated at reflux in an atmosphere of dry nitrogen for 4 hours. The solution was then evaporated under reduced pressure and the residual oil was triturated with a mixture of light petroleum ether (b.p. 40—60°C.) and diethyl ether, to give a white solid. Recrystallisation of this material from a mixture of dichloromethane and diethyl ether gave 5 - phenyl - 2 - oxopentyltriphenylphosphonium chloride (11.2 g.), in the form of a white crystalline solid, m.p. 192—195°C.

[Elemental analysis: C, 76.0; H, 6.2%; $C_{29}H_{28}ClOP$ requires: C, 75.9; H, 6.2%. ν_{max} 1110 cm^{-1}, 1445 cm^{-1}, 1490 cm^{-1}, 1695 cm^{-1}).

By proceeding in a similar manner, but substituting for the 1 - chloro - 5 - phenylpentan - 2 - one used as starting material the appropriate quantities of

1 - chloro - 3 - phenylheptan - 2 - one,

1 - chloro - 3 - phenylhexan - 2 - one,

3 - benzyl - 1 - chloroheptan - 2 - one,

1 - chloro - 3 - *p* - chlorobenzylheptan - 2 - one, and

1 - chloro - 3 - *p* - methylbenzylheptan - 2 - one

[all prepared as hereinafter described in Example 8(iii)], there were prepared

2 - oxo - 3 - phenylheptyltriphenylphosphonium chloride, m.p. 185—187°C.

[Elemental analysis: C, 75.1; H, 6.6; Cl, 8.9%; $C_{31}H_{32}ClOP$, $0.1CH_2Cl_2$ requires: C, 75.5; H, 6.5; Cl, 8.6%. ν_{max} 1710 cm^{-1}, 1445 cm^{-1}, 1490 cm^{-1}, 1690 cm^{-1}),

2 - oxo - 3 - phenylhexyltriphenylphosphonium chloride,

3 - benzyl - 2 - oxoheptyltriphenylphosphonium chloride (ν_{max} 1115 cm^{-1}, 1445 cm^{-1}, 1485 cm^{-1}, 1690 cm^{-1}),

3 - *p* - chlorobenzyl - 2 - oxoheptyltriphenylphosphonium chloride (ν_{max} 1110 cm^{-1}, 1445 cm^{-1}, 1495 cm^{-1}, 1690 cm^{-1}), and

3 - *p* - methylbenzyl - 2 - oxoheptyltriphenylphosphonium chloride (ν_{max} 1110 cm^{-1}, 1445 cm^{-1}, 1490 cm^{-1}, 1695 cm^{-1}), respectively.

(iii) Preparation of chloroketones

4 - Phenylbutanoyl chloride (14.7 g.) was added dropwise to a stirred solution of diazomethane (7.5 g.) in diethyl ether (340 ml.) at 0°C. The solution was stirred in an ice bath for 1 hour further and then it was saturated with anhydrous hydrogen chloride gas. After 1 hour at 0°C, dry nitrogen was passed through this solution, which was then poured onto crushed ice (about 300 ml.). The ethereal layer was separated and the aqueous phase was diluted with water (150 ml.), saturated with sodium chloride, and extracted with diethyl ether. The combined ethereal solutions were washed with water, aqueous sodium carbonate solution (2N), and then again with water, and dried over anhydrous magnesium sulphate. The solution was evaporated and the residue was distilled, to give 1 - chloro - 5 - phenylpentan - 2 - one (11.5 g.), b.p. 150—151°C./10 mm.Hg.

[Elemental analysis: C, 67.4; H, 7.1; Cl, 18.0%; $C_{11}H_{13}OCl$ requires C, 67.2; H, 6.7; Cl, 18.0%. ν_{max} 1455 cm^{-1}, 1500 cm^{-1}, 1725 cm^{-1}].

By proceeding in a similar manner, but replacing the 4-phenylbutanoyl chloride used as starting material by the appropriate quantities of 2 - phenylhexanoyl chloride, 2 - phenylpentanoyl chloride, 2 - benzylhexanoyl chloride, 2 - *p* - chlorobenzylhexanoyl chloride and 2 - *p* - methylbenzylhexanoyl chloride [these last three compounds all prepared as hereinafter described in Example 8(iv)], there were prepared

1 - chloro - 3 - phenylheptan - 2 - one, b.p. 146—148°C./8 mm. Hg.

[Elemental analysis: C, 69.0; H, 7.9%; $C_{13}H_{17}ClO$ requires: C, 69.5; H, 7.6%. ν_{max} 1455 cm^{-1}, 1500 cm^{-1}, 1725 cm^{-1}),

1 - chloro - 3 - phenylhexan - 2 - one (ν_{max} 1400 cm^{-1}, 1455 cm^{-1}, 1495 cm^{-1}, 1720 cm^{-1}],

3 - benzyl - 1 - chloroheptan - 2 - one, b.p. 172—177°C./14 mm.Hg.

[Elemental analysis: C, 70.6; H, 8.3%; $C_{14}H_{19}ClO$ requires: C, 70.4; H, 8.0%. ν_{max} 1400 cm^{-1}, 1455 cm^{-1}, 1500 cm^{-1}, 1715 cm^{-1}],

1 - chloro - 3 - *p* - chlorobenzylheptan - 2 - one, b.p. 196—200°C./13 mm.Hg. (ν_{max} 1410 cm^{-1}, 1465 cm^{-1}, 1495 cm^{-1}, 1715 cm^{-1}), and

1 - chloro - 3 - *p* - methylbenzylheptan - 2 - one, b.p. 182—190°C./13 mm.Hg.

[Elemental analysis: C, 70.8; H, 8.4%; $C_{15}H_{21}ClO$ requires: C, 71.2; H, 8.4%. ν_{max} 1395 cm^{-1}, 1455 cm^{-1}, 1515 cm^{-1}, 1715 cm^{-1}], respectively.

(iv) Preparation of acid chlorides

2 - Benzylhexanoic acid (25.0 g.) and thionyl chloride (50 ml.) were heated together at reflux for 5 hours. Excess thionyl chloride was then removed by evaporation and the residue was distilled, to give 2-benzylhexanoyl chloride (23.6 g.), in the form of a yellow oil, b.p. 147—149°C./10 mm. Hg.

[Elemental analysis: C, 69.4; H, 7.8; Cl, 15.7%, $C_{13}H_{17}ClO$ requires C, 69.5; H, 7.6; Cl, 15.8%. ν_{max} 1500 cm^{-1}, 1605 cm^{-1}, 1780 cm^{-1}].

By proceeding in a similar manner, but substituting 2 - *p* - chlorobenzylhexanoic acid and 2 - *p* - methylbenzylhexanoic acid [both prepared as hereinafter described in Example 8(v)] for the 2 - benzylhexanoic acid, there were prepared 2 - *p* - chlorobenzylhexanoyl chloride, b.p. 179—181°C./10 mm.Hg.

[Elemental analysis: C, 60.4; H, 6.4%; $C_{13}H_{16}Cl_2O$ requires: C, 60.2; H, 6.4%. ν_{max} 1495 cm^{-1}, 1595 cm^{-1}, 1785 cm^{-1}], and

2 - *p* - methylbenzylhexanoyl chloride, b.p. 160—162°/10 mm.Hg. (ν_{max} 1390 cm^{-1}, 1520 cm^{-1}, 1790 cm^{-1}), respectively.

(v) Preparation of acids

(a) Preparation of diethyl 2 - *p* - chlorobenzyl - 2 - butylmalonate

p - Chlorobenzyl chloride (88.0 g.) was added to a stirred solution of diethyl 2 - butylmalonate (108.0 g.) in dry ethanol (500 ml.) containing sodium (11.5 g.). The mixture was heated at reflux for 6 hours, then filtered and the filtrate concen-

trated *in vacuo* to remove the ethanol. Water (150 ml.) was added to the residue and the resulting mixture was extracted with diethyl ether. The ethereal solution was dried over anhydrous magnesium sulphate and then evaporated and the residue was distilled, to give diethyl 2 - *p* - chlorobenzyl - 2 - butylmalonate (110.0 g.), in the form of a colourless oil, b.p. 180—182°C./1.0 mm. Hg.

[Elemental analysis: C, 63.3; H, 7.5, Cl, 10.5%; $C_{18}H_{25}ClO_4$ requires C, 63.4; H, 7.4; Cl, 10.4%].

(b) Preparation of 2 - *p* - chlorobenzylhexanoic acid

A mixture of diethyl 2 - *p* - chlorobenzyl - 2 - butylmalonate (110 g.) and sodium hydroxide (103 g.) in water (100 ml.) and ethanol (400 ml.) was stirred and heated at reflux for 21 hours. The ethanol was removed under reduced pressure, water was added to the residue and the resulting solution was washed with diethyl ether. The aqueous solution was brought to pH 1 by the addition of concentrated hydrochloric acid and the oil which separated was extracted with diethyl ether. After being washed with water the ethereal solution was dried over anhydrous magnesium sulphate and then evaporated, and the residual oil was heated in a metal bath at 200°C, for 20 minutes until the evolution of carbon dioxide was complete. The residue was distilled, to give 2 - *p* - chlorobenzylhexanoic acid (63.6 g.), in the form of a colourless oil, b.p. 212—214°C./12 mm. Hg.

[Elemental analysis: C, 65.4; H, 7.3; Cl, 14.7%, $C_{13}H_{17}ClO_2$ requires: C, 64.9; H, 7.1; Cl, 14.7%].

By proceeding in a similar manner, but substituting *p* - methylbenzyl chloride for the *p* - chlorobenzyl chloride used as starting material, there were prepared diethyl 2 - *p* - methylbenzyl - 2 - butylmalonate, b.p. 196—198°C./10 mm.Hg.

[Elemental analysis: 71.3; H, 9.0%; $C_{19}H_{28}O_4$ requires: C, 71.2; H, 8.8%] and 2 - *p* - methylbenzylhexanoic acid, b.p. 195—198°C./10 mm.Hg.

[Elemental analysis: C, 76.7; H, 9.5%; $C_{14}H_{20}O_2$ requires: C, 76.3; H, 9.15%], respectively.

EXAMPLE 9

Dimethyl 2 - oxoalkylphosphonates

A solution of butyl lithium (9.6 g.) in hexane (97 ml.) and anhydrous diethyl ether (160 ml.) was added during 20 minutes to a stirred solution of dimethyl methylphosphonate (18.6 g.) in anhydrous tetrahydrofuran (80 ml.) at −50°C., in an atmosphere of nitrogen. The solution was stirred for a further 15 minutes at −60°C, and then a solution of ethyl β - phenylpropionate (13.4 g.) in anhydrous tetrahydrofuran (60 ml.) was added during 10 minutes at −60°C. This solution was stirred at −60°C. for 90 minutes and then at the ambient temperature for 150 minutes. Glacial acetic acid (14.2 ml.) was then added and the solvents were evaporated off. Water (75 ml.) was added to the gelatinous residue and then the mixture was extracted with diethyl ether. The ethereal extracts were washed with water, dried over anhydrous magnesium sulphate and the ether was then removed *in vacuo*.

The residue was distillated, to give dimethyl 2 - oxo - 4 - phenylbutylphosphonate (10.7 g.), in the form of a colourless oil, b.p. 155—158°C./0.1 mm.Hg.

[Elemental analysis: C, 56.4; H, 6.9; P, 11.8%; $C_{12}H_{17}O_4P$ requires: C, 56.25; H, 6.7; P, 12.1%. ν_{max} 835 cm^{-1}, 1035 cm^{-1}, 1180 cm^{-1}, 1260 cm^{-1}, 1455 cm^{-1}, 1710 cm^{-1}].

By proceeding in a similar manner, but replacing the ethyl β - phenylpropionate used as a starting material by the appropriate quantities of ethyl phenylacetate and ethyl 2 - (2 - phenylethyl)hexanoate, there were prepared dimethyl 2 - oxo - 3 - phenylpropylphosphonate (b.p. 143—150°C./0.1 mm.Hg;

[Elemental analysis: C, 54.6; H, 6.3%; $C_{11}H_{15}O_4P$ requires: C, 54.5; H, 6.2%. ν_{max} 835 cm^{-1}, 1035 cm^{-1}, 1180 cm^{-1}, 1260 cm^{-1}, 1455 cm^{-1}, 1710 cm^{-1}] and dimethyl 2 - oxo - 3 - (2 - phenylethyl)heptylphosphonate (b.p. 162—172°C./0.15 mm.Hg.

[Elemental analysis: C, 62.6; H, 8.6; P, 9.3%; $C_{17}H_{27}O_4P$ requires: C, 62.6; H, 8.3; P, 9.5%. ν_{max} 810 cm^{-1}, 1030 cm^{-1}, 1180 cm^{-1}, 1260 cm^{-1}, 1455 cm^{-1}, 1700 cm^{-1}], respectively.

The ethyl 2 - (2 - phenylethyl)hexanoate, used as a starting material, was prepared by heating at reflux for 18 hours a solution of 2 - (2 - phenylethyl)hexanoic acid (17.0 g.) in anhydrous ethanol (15.5 ml.) and concentrated sulphuric acid (1.5 ml.). The solution was then added to water (150 ml.) and the oil which separated was extracted with diethyl ether. The ethereal solution was washed successively with water, aqueous sodium carbonate solution (2N) and water, and then dried over anhydrous magnesium sulphate and evaporated. The residue was distilled, to give

ethyl 2 - (2 - phenylethyl)hexanoate (15.25 g.), in the form of a colourless oil, b.p. 158—160°C./7 mm.Hg.

[Elemental analysis: C, 77.5; H, 9.9%; $C_{16}H_{24}O_2$ requires: C, 77.4; H, 9.7%].

EXAMPLE 10

By proceeding in the manner hereinbefore described in Example 5(i) and (ii), but replacing the 7 - {1,4 - dioxa - 7 - (3 - oxo - 5 - phenylpent - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid used as starting material in Example 5(ii) by the appropriate quantity of 7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenoxybut - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid (preparated as hereinafter described), there were prepared

7 - {1,4 - dioxa - 7 - (3 - hydroxy - 4 - phenoxybut - *trans* - 1 - enyl)spiro-[4,4]non - 6 - yl}heptanoic acid (ν_{max} 950 cm^{-1}, 975 cm^{-1}, 1700 cm^{-1}, 3400 cm^{-1}) and

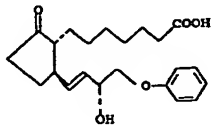
7 - [5 - (3 - hydroxy - 4 - phenoxybut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

[Elemental analysis: C, 70.6; H, 8.1%; $C_{22}H_{30}O_5$ requires: C, 71.0; H, 8.0%. ν_{max} 970 cm^{-1}, 1700 cm^{-1}, 1720 cm^{-1}.]

N.M.R. (approximately 10% w/v solution in deuterochloroform): multiplets at 1.0—2.0δ, 2.0—2.8δ, 3.8—4.1δ, 4.4—4.7δ, 5.7—5.9δ and 6.8—7.6δ].

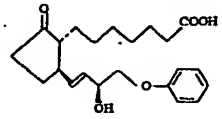
The 7 - [5 - (3 - hydroxy - 4 - phenoxybut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid (0.55 g.) was separated, by preparative thin layer chromatography on silica gel plates, using a mixture of ethyl acetate, cyclohexane and 90% formic acid (200:200:5 by volume) as the eluant and eluting each plate four times, to produce two diastereoisomeric components.

By analogy with known prostaglandins the material (80 mg.) closer to the origin (component "10a") was thought to be a 1:1 mixture of the isomer



and its enantiomer

[Elemental analysis C, 70.8; H, 8.0%] while the material (103 mg.) farther from the origin ("component 10b") was thought to a 1:1 mixture of the isomer



and its enantiomer

[Elemental analysis: C, 70.4; H, 8.4%].

The 7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenoxybut - *trans* - 1 - enyl)spiro[4,4]-non - 6 - yl}heptanoic acid, used as starting material, was prepared by proceeding in a similar manner to that described hereinbefore in Example 1(ii) and (iii)(b) but replacing the benzoylmethylenetriphenylphosphorane used as a starting material by the appropriate quantity of 3 - phenoxy - 2 - oxopropylidenetriphenylphosphorane, to product 6 - (7 - hydroxyheptyl) - 7 - (3 - oxo - 4 - phenoxybut - *trans* - 1 - enyl) - 1,4 - dioxaspiro[4,4]nonane and 7 - {1,4 - dioxa - 7 - (3 - oxo - 4 - phenoxybut - *trans* - 1 - enyl)spiro[4,4]non - 6 - yl}heptanoic acid respectively.

The 3 - phenoxy - 2 - oxopropylidenetriphenylphosphorane, used as a starting material, was prepared as follows:—

A solution of 1 - chloro - 3 - phenoxyacetone (6.8 g.) and triphenylphosphine (12 g.) in chloroform (16 ml.) was saturated with nitrogen and heated at reflux under nitrogen overnight. An excess of dry diethyl ether was added, and then the solvents were decanted from the gum that separated. The remaining solvent was removed *in vacuo*, to give crude 2 - oxo - 3 - phenoxypropyltriphenylphosphonium chloride (10.35 g.). This was stirred vigorously with a solution of sodium carbonate (18 g.) in water (180 ml.) for 24 hours. The solution was extracted with diethyl ether and the ethereal extracts dried over sodium sulphate. The solvent was removed by evaporation, to give 3 - phenoxy - 2 - oxopropylidenetriphenylphosphorane (5.3 g.), a sticky solid.

The 1 - chloro - 3 - phenoxyacetone, used as a starting material, was prepared as follows: —

8N Jones reagent (100 ml.) was added dropwise to a stirred solution of 1 - chloro - 3 - phenoxy - 2 - propanol (28.3 g.) in acetone (100 mL) during 1 hour while maintaining the reaction temperature at 20°C. The mixture was then stirred for 4 hours, and then sufficient water was added to dissolve the precipitated chromium salts. The mixture was extracted three times with diethyl ether and the combined ethereal extracts were dried over sodium sulphate, concentrated under reduced pressure, dried again over sodium sulphate, and concentrated further and distilled, to give 1 - chloro - 3 - phenoxyacetone (13.9 g.), b.p. 150—155°C./20 mm.Hg.

By proceeding in a manner similar to that hereinbefore described, for example in the foregoing Examples, there were prepared the following compounds of formula I: —

7 - [5 - (3 - oxo - 6 - phenylhex - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid (ν_{max} 975 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1700 cm^{-1} 1730 cm^{-1});

7 - [5 - (3 - oxo - 4 - phenylbut - *trans* - enyl) - 2 - oxocyclopentyl]heptanoic acid (ν_{max} 990 cm^{-1}, 1625 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1});

7 - {5 - [5 - (2,4 - dichlorophenyl) - 3 - oxopent - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid (ν_{max} 985 cm^{-1}, 1625 cm^{-1}, 1665 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1});

7 - [5 - (4 - *p* - bromophenyl - 3 - oxobut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid (ν_{max} 985 cm^{-1}, 1620 cm^{-1}, 1700 cm^{-1}, 1725 cm^{-1});

7 - [5 - (4 - *m* - trifluoromethylphenyl - 3 - oxobut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid (ν_{max} 990 cm^{-1}, 1335 cm^{-1}, 1630 cm^{-1}, 1710 cm^{-1}, 1740 cm^{-1});

7 - {5 - [3 - (naphth - 2 - yl) - 3 - oxoprop - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid,

[Elemental analysis: C, 76.7; H, 7.5%; $C_{25}H_{28}O_4$ requires C, 76.5; H, 7.2%. ν_{max} 900 cm^{-1}, 1620 cm^{-1}, 1660 cm^{-1}, 1700 cm^{-1}, 1730 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlets at 9.2δ and 7.16δ, doublet at 7.1δ (J=2 cycles/second), multiplets at 7.5—8.6δ, 2.0—2.6δ and 1.0—2.0δ];

7 - {5 - [3 - hydroxy - 3 - (naphth - 2 - yl)propyl] - 2 - oxocyclopentyl}-heptanoic acid,

[Elemental analysis: C, 75.4; H, 8.3%; $C_{28}H_{32}O_4$ requires C, 75.7; 8.1%. ν_{max} 1705 cm^{-1}, 1720 cm^{-1}, 3400 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlet at 6.73δ, multiplets at 7.3—8.0δ, 4.82δ, 1.6—2.6δ, 1.0—2.0δ];

7 - [5 - (3 - acetoxy - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid,

[Elemental analysis: C, 72.6; H, 8.3%; $C_{25}H_{34}O_5$ requires C, 72.4; H, 8.3%. ν_{max} 1240 cm^{-1}, 1705 cm^{-1}, 1730 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlet at 7.24δ, multiplets at 5.5—5.8δ, 5.0—5.5δ, 1.0—3.0δ and 2.05δ];

7 - {5 - [3 - acetoxy - 3 - (naphth - 2 - yl)propyl] - 2 - oxocyclopentyl}heptanoic acid,

[Elemental analysis: C, 74.3; H, 8.0%; $C_{27}H_{34}O_5$ requires C, 73.9; H, 7.8%. ν_{max} 1240 cm^{-1}, 1705 cm^{-1}, 1720 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlets at 9.4δ and 2.1δ, triplet at 5.93δ (J=6 cycles/second), multiplets at 7.3—8.0δ, 1.8—2.6δ and 1.0—2.0δ];

undecyl 7 - [5 - (3 - acetoxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoate,

[Elemental analysis: C, 75.5; H, 10.3%; $C_{34}H_{54}O_5$ requires C, 75.2; H, 10.0%. ν_{max} 1230 cm^{-1}, 1725 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlets at 7.37δ and 2.10δ, triplets at 5.8δ (J=6 cycles/second), 4.08δ, (J=6.5 cycles/second), 0.9δ (J=5 cycles/second), multiplets at 1.0—2.5δ];

methyl 7 - [5 - (3 - oxo - 4 - phenylbutyl) - 2 - oxocyclopentyl]heptanoate

[Elemental analysis: C, 73.9; H, 9.1%; $C_{23}H_{32}O_4$ requires C, 74.2; H, 8.7%. ν_{max} 1730 cm^{-1}.

N.M.R. (approximately 10% w/v solution in deuterochloroform): singlets at 7.24δ, 3.69δ and 3.64δ, multiplets at 1.0—2.8δ];

7 - [5 - (3 - oxo - 4 - phenylbutyl) - 2 - oxocyclopentyl]heptanoic acid (ν_{max} 1705 cm^{-1}, 1730 cm^{-1});

A 1:1 mixture of 11 - deoxy - 16 - (4 - methylbenzyl)prostaglandin E_1 and its enantiomer [ν_{max} 975 cm^{-1}, 1705 cm^{-1}, 1730 cm^{-1}, 3400 cm^{-1}];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - (4 - methylbenzyl)prostaglandin E_1 and its enantiomer
[I.R. spectrum virtually identical with that of the above epimeric material];
A 1:1 mixture of 11 - deoxy - 16 - (4 - propoxyphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer
[N.M.R. (approximately 10% w/v solution in deuterochloroform): triplet at 1.0δ (J=7 cycles/second), multiplets at 1.1—2.7δ, 3.8—4.0δ, 4.3—4.7δ, 5.7—5.9δ and a singlet at 6.85δ];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - (4 - propoxyphenoxy - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[Elemental analysis: C, 69.5; H, 9.0; $C_{25}H_{36}O_6$ requires C, 69.4; H, 8.4%.
N.M.R. spectrum virtually identical with that of the above epimeric material];
A 1:1 mixture of 11 - deoxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[Elemental analysis: C, 62.8; H, 6.85%; $C_{23}H_{29}O_5F_3$ requires C, 62.4; H, 6.61%.
N.M.R. (approximately 10% w/v solution in deuterochloroform); multiplets at 1.1—2.7δ, 3.9—4.1δ, 4.4—4.7δ, 5.7—5.9δ, broad singlet at 6.0—6.3δ and a multiplet at 7.0—7.6δ];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[Elemental analysis: C, 62.1; H, 6.81%.
N.M.R. spectrum virtually identical with that of the above epimeric material];
A 1:1 mixture of 11 - deoxy - 16 - (4 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[Elemental analysis: C, 64.6; H, 7.3%; $C_{22}H_{29}ClO_5$ requires : C, 64.6; H, 7.1; Cl, 8.7%.
N.M.R. (approximately 10% w/v solution in deuterochloroform): multiplets at 1.1—2.7δ, 3.7—4.2δ, 4.4—4.8δ, 5.7—5.9δ, 6.6—7.5δ];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - (4 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[Elemental analysis: C, 64.2; H, 7.3; Cl, 9.0%.
N.M.R. spectrum virtually identical with that of the above epimeric material];
A 1:1 mixture of 11 - deoxy - 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[N.M.R. (approximately 10% w/v solution in deuterochloroform): multiplets at 0.9—2.5δ, 3.7—4.1δ, 4.2—4.7δ, 5.0—5.9δ, 6.7—7.2δ];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[N.M.R. spectrum virtually identical with that of the above epimeric material];
A 1:1 mixture of 11 - deoxy - 16 - (2 - methylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[Elemental analysis C, 71:1; H, 8.5%; $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%.
N.M.R. (approximately 10% w/v solution in deuterochloroform): multiplets at 0.5—2.8δ, 3.7—4.0δ, 4.2—4.7δ, 4.8—5.3δ 5.6—5.9δ, 6.6—7.3δ];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - (2 - methylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1 and its enantiomer,
[N.M.R. spectrum virtually identical with that of the above epimeric material];
A 1:1 mixture of 11 - deoxy - 16 - phenoxy - 17,18,19,20 - tetranorprostaglandin E_1 methyl ester and its enantiomer,
[Elemental analysis: C, 71.0; H, 8.3%; $C_{23}H_{32}O_6$ requires: C, 71.1; H, 8.3%.
N.M.R. (approximately 10% w/v solution in deuterochloroform): singlet 3.7δ, multiplets at 1.2—2.8δ, 3.9—4.1δ, 4.3—4.6δ, 5.7—5.9δ, 6.8—7.5δ];
A 1:1 mixture of 15 - *epi* - 11 - deoxy - 16 - phenoxy - 17,18,19,20 - tetranorprostaglandin E_1 methyl ester and its enantiomer,
[Elemental analysis: C, 71.4; H, 8.7%
N.M.R. spectrum virtually identical with that of the above epimeric material];
7 - {5 - [5 - (3 - trifluoromethylphenyl) - 3 - oxopent - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid [ν_{max} 800 cm^{-1}, 985 cm^{-1}, 1125 cm^{-1}, 1165 cm^{-1}, 1330 cm^{-1}, 1630 cm^{-1}, 1705 cm^{-1} and 1740 cm^{-1}];
7 - {5 - [5 - (4 - fluorophenyl) - 3 - oxopent - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid [ν_{max} 830 cm^{-1}, 985 cm^{-1}, 1630 cm^{-1}, 1705 cm^{-1}, and 1740 cm^{-1}].

The present invention includes within its scope pharmaceutical compositions which comprise at least one compound of the invention together with a pharmaceutical carrier or coating. In clinical practice the compounds of the present invention will normally be administered orally, rectally, vaginally or parenterally.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules.

Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs.

The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing one or more of the compounds of the invention.

Solid compositions for vaginal administration include pessaries.

Solid compositions for rectal administration include suppositories.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions.

The compounds of the invention may alternatively be administered orally by any method known *per se* for administration by inhalation of drugs which are not themselves gaseous under normal conditions of administration. Thus, a solution of the active ingredient in a suitable pharmaceutically-acceptable solvent, for example water, can be nebulized by a mechanical nebulizer, for example a Wright Nebulizer, to give an aerosol of finely-divided liquid particles suitable for inhalation. The active ingredients may also be administered orally by inhalation in the form of aerosols generated from self-propelling pharmaceutical compositions.

Methods of presentation of pharmaceutically active compounds are well known in the art and a suitable vehicle may be determined by the physician, pharmacist or veterinarian, depending upon such factors as the effect sought, the size, age, sex and condition of the patient and, for veterinary uses, species of the animal to be treated, and on the physical properties of the active compound. The compositions may also contain, as is usual in the art, such materials as solid or liquid diluents, wetting agents, preservatives, flavouring and colouring agents and the like.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage for the therapeutic effect desired shall be obtained. Obviously several unit dosage forms may be administered at about the same time.

In general, the compositions should normally contain at least 0.025% by weight of active substance when required for administration by injection; for oral administration the preparations will normally contain at least 0.1% by weight of active substance. The dose employed depends upon the desired therapeutic effect, the route of administration and the duration of the treatment. In the adult, the doses are generally, for example, between 0.02 and 2.0 mg. by aerosol administration, between 0.0002 and 2.0 mg./kg. body weight by intravenous administration, and between 0.001 and 1.0 mg./kg. body weight orally. If necessary these doses may be repeated as and when required.

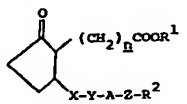
The following Example illustrates pharmaceutical compositions according to the invention.

EXAMPLE 11

7 - [5 - (3 - Hydroxy - 4 - phenoxybut - *trans* - 1 - enyl) - 2 - oxocyclopentyl] - heptanoic acid (300 mg.) was dissolved in ethanol (1 ml.) and the solution obtained was added to an aqueous solution (12 ml.) containing sodium carbonate (50 mg.). Aqueous sodium chloride solution (0.9% w/v; 2 ml.) was then added to give a final volume of 15 ml. The solution was then sterilized by passage through a bacteria-retaining filter and placed in 1.5 ml. portions in 5 ml. ampoules, to give 30 mg. of the heptanoic acid derivative (in the form of its sodium salt) per ampoule. The contents of the ampoules were freeze-dried and the ampoules sealed. Dissolution of the contents of an ampoule in a suitable volume, e.g. 2 ml. of sterile water or physiological saline, gave a solution ready for administration by injection.

WHAT WE CLAIM IS:—

1. Cyclopentane derivatives of the general formula:—



[wherein R^1 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms, R^2 represents an aryl or heterocyclyl group, which may be substituted by one or more substituents selected from halogen atoms, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms, trihalomethyl groups, alkenyl groups containing from 2 to 4 carbon atoms, phenyl groups, alkoxy groups containing from 1 to 4 carbon atoms, hydroxy groups, nitro groups, cyano groups, carboxy groups, alkoxycarbonyl groups wherein the alkoxy moiety contains from 1 to 4 carbon atoms, hydroxymethylene groups, alkoxymethylene groups wherein the alkoxy moiety contains from 1 to 4 carbon atoms, sulphino groups, alkylsulphonyl groups wherein the alkyl moiety contains from 1 to 4 carbon atoms, and sulphamoyl, carbamoyl, N - aminocarbamoyl, amidino, amino and hydroxyamino groups, each such nitrogen-containing group optionally being substituted by one or more alkyl groups each containing from 1 to 4 carbon atoms, *n* represents 5, 6, 7 or 8, and either

(i) A represents a straight- or branched-alkylene chain containing from 1 to 12 carbon atoms, X represents an ethylene or *trans*-vinylene group, Y represents a carbonyl group or a group —CH(OR³)— (wherein R^3 represents a hydrogen atom or a carboxylic acyl group), and Z represents a direct bond or an oxygen or sulphur atom, or else

(ii) A and Z both represent direct bonds, and X and Y represent simultaneously ethylene and carbonyl, *trans*-vinylene and carbonyl, or ethylene and —CH(OR³)—, groups respectively (R^3 being as hereinbefore defined)] and, when R^1 represents a hydrogen atom, non-toxic salts thereof.

2. Cyclopentane derivatives according to claim 1 wherein R^2 represents an aryl or heterocyclyl group, which may be substituted by one or more substituents selected from halogen atoms, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms, and trihalomethyl groups, and R^1, *n*, A, X, Y and Z are as defined in claim 1, and, when R^1 represents a hydrogen atom, non-toxic salts thereof.

3. Cyclopentane derivatives according to claim 1 or 2 wherein *n* represents 6.

4. Cyclopentane derivatives according to claim 1, 2 or 3 wherein R^1 represents a straight- or branched-chain alkyl group containing from 1 to 12 carbon atoms.

5. Cyclopentane derivatives according to any one of claims 1 to 4 wherein R^2 represents a substituted or unsubstituted heterocyclyl or aryl (other than phenyl) group or a substituted phenyl group, the substituents present on said substituted heterocyclyl and aryl (including phenyl) groups being as specified in claim 1 or 2.

6. Cyclopentane derivatives according to claim 1, 2, 4 or 5 wherein *n* represents 5, 7 or 8.

7. Cyclopentane derivatives according to any one of the preceding claims wherein X represents an ethylene group.

8. Cyclopentane derivatives according to any one of the preceding claims wherein Y represents a carbonyl group.

9. Cyclopentane derivatives according to any one of the preceding claims wherein A represents a direct bond.

10. Cyclopentane derivatives according to any one of the preceding claims wherein Z represents an oxygen or sulphur atom.

11. Cyclopentane derivatives according to any one of the preceding claims wherein R^2 represents a phenyl, naphthyl, furyl or thienyl group unsubstituted or substituted as specified in claim 1 or 2.

12. Cyclopentane derivatives according to any one of claims 1 to 10 wherein R^2 represents a phenyl, naphthyl or thienyl group unsubstituted or substituted as specified in claim 1 or 2.

13. Cyclopentane derivatives according to any one of claims 1 to 8, 10, 11 and 12 wherein A represents a straight- or branched-alkylene chain containing from 1 to 7 carbon atoms.

14. Cyclopentane derivatives according to any one of claims 1 to 7 and 9 to 13 wherein Y represents a group —CH(OR³)—, wherein R^3 represents a hydrogen atom or a straight- or branched-chain alkanoyl group containing from 1 to 6 carbon atoms, or a benzoyl group.

15. Alkali metal, ammonium and non-toxic amine salts of a cyclopentane derivative as claimed in any one of claims 1 to 3 and 5 to 14 wherein R^1 represents a hydrogen atom.

16. 7 - [5 - (3 - Oxo - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

17. 7 - [5 - (3 - Oxo - 4 - phenylbut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

18. 7 - [5 - (3 - Oxo - 3 - phenylprop - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

19. 7 - [5 - (3 - Oxo - 6 - phenylhex - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

20. 7 - [5 - (3 - Oxo - 4 - phenylhept - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

21. 7 - [5 - (3 - Oxo - 4 - phenyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

22. 7 - [5 - (4 - Benzyl - 3 - oxooct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

23. 7 - [5 - (4 - *p* - Chlorobenzyl - 3 - oxooct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

24. 7 - [5 - (4 - *p* - Methylbenzyl - 3 - oxooct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

25. 7 - [5 - (3 - *p* - Bromophenyl - 3 - oxoprop - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

26. 7 - [5 - (3 - Oxo - 3 - thien - 2′ - ylprop - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

27. 7 - {5 - [4 - (2 - Phenylethyl) - 3 - oxooct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

28. 7 - [5 - (3 - Hydroxy - 4 - phenyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

29. 7 - [5 - (4 - *p* - Chlorobenzyl - 3 - hydroxyoct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

30. 7 - [5 - (4 - *p* - Methylbenzyl - 3 - hydroxyoct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

31. 7 - {5 - [3 - Hydroxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

32. 7 - [5- (3 - Hydroxy - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

33. 7 - [5 - (3 - Hydroxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid.

34. 7 - [5 - (3 - Acetoxy - 4 - *p* - methylbenzyloct - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

35. 7 - [5 - (3 - Acetoxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]heptanoic acid.

36. 7 - {5 - [3 - Acetoxy - 4 - (2 - phenylethyl)oct - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

37. 7 - [5 - (3 - Hydroxy - 4 - phenoxybut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

38. 7 - [5 - (3 - Oxo - 6 - phenylhex - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

39. 7 - [5 - (3 - Oxo - 4 - phenylbut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

40. 7 - {5 - [5 - (2,4 - Dichlorophenyl) - 3 - oxopent - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

41. 7 - [5 - (4 - *m* - Trifluoromethylphenyl - 3 - oxobut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

42. 7 - {5 - [3 - (Naphth - 2 - yl) - 3 - oxoprop - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

43. 7 - {5 - [3 - Hydroxy - 3 - (naphth - 2 - yl)propyl] - 2 - oxocyclopentyl}-heptanoic acid.

44. 7 - [5 - (3 - Acetoxy - 5 - phenylpent - *trans* - 1 - enyl) - 2 - oxocyclopentyl]-heptanoic acid.

45. 7 - {5 - [3 - Acetoxy - 3 - (naphth - 2 - yl)propyl] - 2 - oxocyclopentyl}-heptanoic acid.

46. 7 - [5 - (3 - Oxo - 4 - phenylbutyl) - 2 - oxocyclopentyl]heptanoic acid.

47. 7 - [5 - (4 - *p* - Bromophenyl - 3 - oxobut - *trans* - 1 - enyl) - 2 - oxocyclopentyl]heptanoic acid.

48. 11 - Deoxy - 16 - (4 - methylbenzyl)prostaglandin E_1.

49. 15 - *Epi* - 11 - deoxy - 16 - (4 - methylbenzyl)prostaglandin E_1.

50. 11 - Deoxy - 16 - (4 - propoxyphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

51. 15 - *Epi* - 11 - deoxy - 16 - (4 - propoxyphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

52. 11 - Deoxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

53. 15 - *Epi* - 11 - deoxy - 16 - (3 - trifluoromethylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

54. 11 - Deoxy - 16 - (4 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

55. 15 - *Epi* - 11 - deoxy - 16 - (4 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

56. 11 - Deoxy - 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

57. 15 - *Epi* - 11 - deoxy - 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

58. 11 - Deoxy - 16 - (2 - methylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

59. 15 - *Epi* - 11 - deoxy - 16 - (2 - methylphenoxy) - 17,18,19,20 - tetranorprostaglandin E_1.

60. 7 - {5 - [5 - (3 - Trifluoromethylphenyl) - 3 - oxopent - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

61. 7 - {5 - [5 - (4 - Fluorophenyl) - 3 - oxopent - *trans* - 1 - enyl] - 2 - oxocyclopentyl}heptanoic acid.

62. Undecyl 7 - [5 - (3 - acetoxy - 3 - phenylpropyl) - 2 - oxocyclopentyl]-heptanoate.

63. Methyl 7 - [5 - (3 - oxo - 4 - phenylbutyl) - 2 - oxocyclopentyl]heptanoate.

64. 11 - Deoxy - 16 - phenoxy - 17,18,19,20 - tetranorprostaglandin E_1 methyl ester.

65. 15 - *Epi* - 11 - deoxy - 16 - phenoxy - 17,18,19,20 - tetranorprostaglandin E_1 methyl ester.

66. The enantiomer of a cyclopentane derivative claimed in any one of claims 48 to 59, 64 or 65.

67. A mixture of a cyclopentane derivative claimed in any one of claims 48 to 59, 64 or 65 with its enantiomer.

68. The isomers

and their enantiomers.

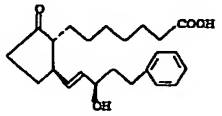
69. A 1:1:1:1 mixture of the isomers depicted in claim 68 and their enantiomers.

70. The isomers

and their enantiomers.

71. A 1:1:1:1 mixture of the isomers depicted in claim 70 and their enantiomers.

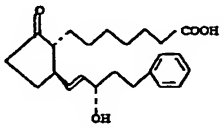
72. The isomer



and its enantiomer.

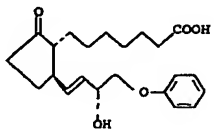
73. A 1:1 mixture of the isomer depicted in claim 72 and its enantiomer.

74. The isomer

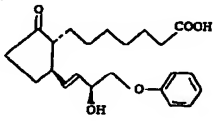


and its enantiomer.

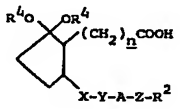
75. A 1:1 mixture of the isomer depicted in claim 74 and its enantiomer.
76. The isomer



and its enantiomer.
77. A 1:1 mixture of the isomer depicted in claim 76 and its enantiomer.
78. The isomer



and its enantiomer.
79. A 1:1 mixture of the isomer depicted in claim 78 and its enantiomer.
80. Non-toxic salts of a cyclopentane derivative as claimed in any one of claims 16 to 61 and 68 to 79.
81. Process for the preparation of cyclopentane derivatives of the general formula depicted in claim 1, wherein R^1 represents a hydrogen atom, Y represents a carbonyl or hydroxymethylene group, and R^2, n, X, A and Z are as defined in claim 1, which comprises the hydrolysis of a compound of the general formula:—



(wherein R^2, n, X, Y, A and Z are as defined in claim 1, and the symbols R^4 represent identical alkyl groups or together form an ethylene linkage unsubstituted or substituted by identical alkyl groups on each carbon atom) by the application or adaptation of known methods for the conversion of a ketal group to a ketone group.
82. Process according to claim 81 wherein the symbols R^4 together represent an unsubstituted ethylene linkage.
83. Process according to claim 81 or 82 in which the hydrolysis is carried out in acidic conditions.
84. Process according to claim 81 or 82 in which the hydrolysis is carried out with a dilute inorganic acid, or with an organic acid in the presence of water.
85. Process according to claim 81, 82, 83 or 84 followed by the step of converting a hydroxymethylene group represented by symbol Y in the cyclopentane product of the general formula depicted in claim 1 into a carboxylic acyloxymethylene group by known methods for the acylation of alcohols.
86. Process according to any one of claims 81 to 85 followed by the step of converting the cyclopentane acid product of the general formula depicted in claim 1 wherein R^1 represents a hydrogen atom into a corresponding compound wherein R^1 represents an alkyl group containing from 1 to 12 carbon atoms by known methods for the esterification of acids.
87. Process according to any one of claims 81 to 85 followed by the step of converting by known methods the cyclopentane acid product of the general formula depicted in claim 1, wherein R^1 represents a hydrogen atom, into a non-toxic salt.
88. Process for the preparation of cyclopentane derivatives of the general formula specified in claim 1 and, when R^1 represents a hydrogen atom, non-toxic salts thereof substantially as hereinbefore described with especial reference to any one of Examples 1 to 7 and 10.
89. Cyclopentane derivatives of the general formula specified in claim 1 and

non-toxic salts thereof when prepared by the process claimed in any one of claims 81 to 88.

90. Pharmaceutical compositions which comprise, as active ingredient, at least one cyclopentane derivative as claimed in any one of claims 1 to 79 or, when appropriate, a non-toxic salt thereof together with a pharmaceutical carrier or coating.

91. Pharmaceutical compositions according to claim 90 substantially as hereinbefore described with particular reference to Example 11.

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